REMARKS

The Office Action of August 27, 2002 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is respectfully requested. Applicants thank the Examiner for his thorough and detailed remarks attached to the most recent Office Action and the entrance of Applicant's submission filed on 6/12/02. Claims 35-43, 56-58, 91-93 and 96-119 are currently pending. Claims 35-43, 56-58 and 91-93 are amended herein. Claims 31, 34, 48-55, 60, 61, 65-73, 86-90 and 94-95 canceled herein. Claims 96 through 119 have been added herein. Applicants thank the Examiner for his notation and acceptance of the current applications' claim of priority to the provisional application filed November 2, 1998. Early and favorable action is earnestly solicited.

Oath and Declaration Objection

The Examiner objected to the format of the prior Oath as defective. In response to this rejection the Applicant attaches to this Response a new Oath and Declaration compliant with 37 CFR § 1.63, especially with regard to the name of the inventor Esmail Behboodi and his signature. Respectfully, Applicant believes that the provision of this new fully executed Oath and Declaration overcomes the Examiners' prior rejection. MPEP §§ 602.01 – 602.03.

Claim Amendments

Applicants wish the Examiner to take note that their representation before the USPTO has recently changed. This change in representation has necessitated a review of the specification and prior prosecution activities by their new attorney. During this review it was determined that substantial amendments to the claims were needed to answer the Examiner's objections and to more fully present the invention for examination. Therefore each of the pending claims have been amended or have been added by Applicant in this Response. The pending claims as provided by Applicant are thus intended to be both part of a fully responsive reply to the Examiner's rejections and fully grounded in the teachings of the specification. MPEP §§ 608.01; 714.

Applicants believe that the amendments which have been made, along with the extensive nature of this response serve to put all the remaining claims in better condition for allowance. This is also true with respect to the canceled claims as well as with the claims which were amended or added. Given the above, it is specifically and respectfully requested that the Examiner enter and allow the claims as amended herein.

Applicant Recognition of the Level of Ordinary Skill in the Art

Applicant recognizes that the level of ordinary skill in the art concerning the instant claims is high. This is supported by the requirement of an understanding of the different abilities, strengths, weaknesses and effects of various protein expression systems, particularly with regard to transgenic animal expression systems and the time required to build a herd of transgenic animals according to the prior art.

Applicant respectfully points to legal precedent in the biotechnology arena to make the case that the expected level of skill in the art is high. Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1340 (Fed. Cir. 2000)("Patents, however, are written to enable those skilled in the art to practice the invention, not the public"); Enzo Biochem v. Calgene, Inc., 188 F.3d 1362 (Fed. Cir.1999); Webster Loom Co. v. Higgins, 105 U.S. 580, 26 L.eD. 1177, 1179 (1882). What this means in practical terms is that the specification is not required to teach every detail of the invention or to perform the function of a technical production manual/specification. The specification need only explain how to make and use the invention without requiring an inordinate amount of experimentation. The fact that experimentation needed may be complex or even repetitive does not necessarily make it undue if a person skilled in the art typically engages in such experimentation, as in the instant field. In re Borkowski, 422 F.2d 904, 164 USPQ 214 (CCPA 1970). Applicants therefore believe that the teachings provided in the specification allow those skilled in the art to practice the invention as recited in the pending claims.

The Rejection Under 35 U.S.C. §112, first paragraph

Claims 31, 34-44, 47-58, 60, 61, 65-73, 86-88 and 90-95 are rejected under 35 U.S.C. §112, first paragraph for failure to enable a person skilled in the art to perform the invention commensurate with the breadth of the claims. This rejection of the claims, as amended, is respectfully traversed.

The test for claim support under the first paragraph of 35 U.S.C. § 112, is whether the disclosure as originally filed reasonably conveys to the artisan that the inventor had possession at the time of the later claimed subject matter, rather than the presence or absence of literal support. Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 227 U.S.P.Q. 177 (Fed Cir. 1985); In re Kaslow, 707 F.2d 1366, 217 U.S.P.Q. 1089 (Fed Cir. 1983). As has been previously stated by the courts:

> "Enablement is a legal issue. The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, hence the specification need not disclose what is well known in the art." In re Myers, 410 F.2d 420, 161 USPQ 668 (CCPA 1969); *and see,* Lindemann Maschinefabrik GMBH v. American Hoist and Derrick Co., 221 U.S.P.Q. 481 (Fed. Cir. 1984).

More to the point, the issue of adequate enablement depends on whether one skilled in the art could reproduce the claimed invention without "undue experimentation." *See,* Wang Labs, Inc. v. Toshiba Corp., 993 F.2d 858, 26 U.S.P.Q.2d 1601 (Fed Cir. 1993); Utter v Hiraga, 845 F.2d 993, 6 U.S.P.Q.2d 1709 (Fed. Cir. 1988). The standard in this inquiry was supplied by the Federal Circuit when that court announced that enablement by a disclosure is not precluded even if some experimentation is required, the only limiting factor is that this experimentation must not be "undue." In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In agreement with the Examiner, Applicant understands that in *Wands* Judge Smith decided that the key word in this formula is "undue" not "experimentation" (Office Action of 8/27/02, page 3, 3rd paragraph) and applied a reasonableness standard, given the nature of the invention and the state of the art when he stated:

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is **merely routine**, or if the specification in question provides **a reasonable amount of guidance with respect to the**

direction in which the experimentation should proceed." Wands at 737 (emphasis added).

It should also be remembered that the court in Wands, after the application of all of the Wands factors, held that the Applicants were entitled to claim an assay using any IgM monoclonal antibody having an affinity of at least $10^9 M^{-1}$ for hepatitis B-surface antigen, Wands ***necessarily therefore*** held that the Applicants were entitled to claim ***any*** protein of this class having ***any*** amino structure among a theoretically infinite number of variations in natural or synthetic proteins, as long as they had the same broadly defined and somewhat inexact functional properties as provided in the claims and the limited working examples provided. Wands at 731-37.

In a broad sense the novelty of the instant patent lies, as expected, in the novel manipulation and engineering of the transgenic somatic cell lines and their use to increase the speed and efficiency of 'building' bio-reactors for a desired transgene. That is, decreasing the time required to develop significant numbers of transgenic animals capable of expressing a desired gene or produce a desired protein through multiple rounds of nuclear transfer. Purified differentiated somatic cell preparations are a part of this, but the complete invention focuses on increasing "the efficiency of production of transgenic animals" and the "accelerated scale-up of a specific transgenic line" (SUMMARY OF THE INVENTION, page 1, lines 8-13)(see also in the Specification; page 1, lines 11-15; page 2, lines 25-29; page 6, lines 12-16; and page 11, lines 25-28) This understanding of the current invention, along with the Federal Circuit's repeated assertions that in the field of biotechnology the level of skill in the art is necessarily a high one, indicates that the enablement requirements for the instant claims are 1) determined not by the public at large but by scientists already trained in many of the basics of the technology and well-versed in standard protocols, and 2) are met here. Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1340 (Fed. Cir. 2000)("Patents, however, are written to enable those skilled in the art to practice the invention, not the public"); Enzo Biochem v. Calgene, Inc., 188 F.3d 1362 (Fed. Cir.1999).

It should also be understood that the Applicants themselves are well respected members of the 'those skilled in the art' and cumulatively have over 100 peer-reviewed publications. (*Curriculum Vitae* upon request). Therefore, in making the determination as to whether the

disclosure requirement is satisfied, the person(s) *skilled* in the art are *presumed* to be aware of all of the relevant literature, including trade publications, textbooks, technical journals, and U.S. patents. Thus, upon the disclosure of the instant invention, and the subsequent allowance of the pending claims, a variety of potential uses for those skilled in the art is provided. These techniques revolve around the increased speed and efficiency in building transgenic herds of animals – 'bioreactors' more quickly as mentioned above. With regard to the nature of the specification in the instant matter, the uses therein disclosed need not be apparent to everyone, all that is required is that enablement, and the potential usefulness of the discovery is communicated to the skilled artisans of the relevant technology. Respectfully the Applicants maintain that this communication was sufficiently performed in the specification. Therefore, the Examiners rejection of the amended claims under 35 U.S.C. § 112, first paragraph, is traversed. Webster Loom Co. v. Higgins, 105 U.S. 580, 26 L.eD. 1177, 1179 (1882).

Given the above, therefore, it must be understood that when the Applicants, as in the instant specification:

provide a working example in a transgenic system;

detail the benefits and methods of optimizing multiple rounds of nuclear transfer for the development of transgenic animals;

detail expression in a mammalian transgenic system;

explain the production of a differentiated somatic cell-line and provide a workable means for its use in nuclear transfer procedures

provide extensive guidance to appropriate protocols throughout the specification – including references to old, well-known, and well understood laboratory protocols;

reference many relevant citations in the literature; and

specify the exogenous proteins that may beneficially be produced by practitioners -

any experimentation that may be necessary, becomes routine.

Respectfully, the practitioner in the field no longer need worry that a certain protocol or procedure for transgenic animal scale-up can work, the Applicants in their everyday activities prove to a certainty that it will. More to the point, the methods recited by the Applicants and the purpose of the application provide a means of making recombinant proteins more quickly than previously possible in quantities adequate to address needs for them around the world.

The protocols disclosed in the specification, provide the public the ability to practice the invention, essentially by providing a detailed map leading towards a goal that has already been reached, regardless of the state of the art prior to the application. In conjunction with the extremely high level of skill in the field, it is clear that the specification, as tempered by the relevant case law discussed above, does enable other workers in the field to make and use the invention recited in the amended claims without "excessive" experimentation. Wands at 740.

In view of the foregoing, it is respectfully submitted that the disclosure provided in the instant specification complies fully with the requirements of § 112, first paragraph in that the description of the various laboratory protocols and methods employed by the Applicants to increase the speed and fidelity in the scale-up of transgenic animal herds without undue experimentation.

It is respectfully suggested therefore that Applicants have shown that independent claims 96 and 91. Dependent claims 35-43, 56-58 and 92-93 being dependent upon and further limiting these independent claims should be allowable for that reason. Reconsideration of the rejection of claims 35-43, 56-58 and 91-93 under 35 U.S.C. § 112, first paragraph is respectfully requested.

New claims 96 - 119 are dependent upon independent amended claims 96 or 91 as the case may be. As they retain all the elements of the amended base claims from which they depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 96 - 119 under 35 U.S.C. § 112, first paragraph, in view of the above amendments and remarks.

The Rejection Under 35 U.S.C. §112, second paragraph

Claims 31, 34-44, 47-58, 60, 61, 65-73, 86-88 and 90-95 are rejected under 35 U.S.C. §112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. This rejection is respectfully traversed. Each of the rejections enunciated by the Examiner under 35 U.S.C. §112, second paragraph have been addressed through specific amendment to each of the relevant claims, particularly to remove references to "heterologous transgenes". The amendments were made to clarify, particularly point out, and distinctly claim the subject matter of the invention.

Claims 31, 34, 48-55, 60, 61, 65-73, 86-90 and 94-95 are canceled herein. Reconsideration of the rejection of amended claims 35-43, 56-58 and 91-93 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

New claims 96 - 119 are dependent upon independent amended claims 96 or 91 as the case may be. As they retain all the elements of the amended base claims from which they depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 96 - 119 under 35 U.S.C. § 112, second paragraph, in view of the above amendments and remarks.

The Rejections Under 35 U.S.C. §102(b) and §102(e)

Archer et al.,

Claims 31, 34-44, 47-58, 60, 61, 65-73, 86-88 and 90-95 are rejected under 35 U.S.C. §102(b) as being anticipated by Archer et al. This rejection of the claims, as amended, is respectfully traversed.

Generally, anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference or embodied in a single prior art device or practice. *See,* In re Spada, 911 F.2d 705, 15 U.S.P.Q.2d 1655 (Fed Cir. 1990); *See also,* Minnesota Min. & Mfg. Co. v. Johnson & Johnson Orthopedics, Inc., 976 F.2d 1559, 24 U.S.P.Q.2d (Fed Cir. 1992). Anticipation requires **both an identity of elements and identity of process**, this Archer et al., is incapable of providing. Tyler Refrigeration v. Kysor Indus. Corp., 777 F.2d 687, 227 U.S.P.Q.177 (Fed Cir. 1986). As was stated by the 9th Circuit:

> "Unless all of the same elements are found in exactly the same situation and united in the same way to perform the identical function in prior pleaded art, there is no anticipation." Stauffer v. Slenderella Systems of California, Inc., 254 F.2d 127, 115 USPQ 347 (9th Cir. 1957).

It must be remembered that for anticipation to be properly found it is necessary that a previous disclosure express the virtually identical presence and function of the claimed methods and assays, thereby putting the invention in the hands of the public to practice. That is, guiding precedent states that if a given reference does not teach how to use the invention to the public, no

anticipation can be found. In re Wilder, 429 F.2d 447, 166 USPQ 545 (C.C.P.A. 1964); In re Brown, 329 F.2d 1006, 141 USPQ 245 (C.C.P.A. 1964); In re LeGrice, 301 F.2d 929, 133 USPQ 365 (C.C.P.A. 1962). This is clearly not done with the Archer reference. Examiner states that a step by step guide to the invention is not necessary if that prior art inherently discloses the invention. While this view is problematic in view of the guiding precedent cited immediately above, the Archer reference does not "inherently" or even inferentially disclose the instant invention, or read on any of its amended claims. Moreover, to anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. Mehl/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362; 52 U.S.P.Q.2D 1303 (1999).

Therefore, in order to avoid rejection for anticipation, it is only necessary to show that independent base claims 91 and 96 each contain at least one element not disclosed in Archer et al. In reviewing the teachings of the Archer et al., reference, as guided by the prior legal precedent cited above, it is clear that the claims not only fail to recite the same elements, the actual function or "process" of utilizing the elements differs considerably. Rather, Archer recites "a transgenic goat" derived from using a single round of transfection with "replication defective retrovirus" and actually "targeting these replication-defective retroviruses to mammary epithelial cells" none of which resemble, replace or suggest any of the elements present in the instant application and recited in the claims. Moreover, claim 91 recites several elements not present or suggested in any of the teachings of Archer et al., including:

a) performing a nuclear transfer procedure with said non-human differentiated somatic cells to produce at least one transgenic mammal at least heterozygous for said first DNA sequence;

b) inseminating a first female non-human mammal recipient with semen from a transgenic non-human animal of the same species known to have a transgene present and expressed;

and

c) obtaining a transgenic non-human embryo from said first female recipient;

None of the elements a-c above are disclosed in the Archer et al., reference. Therefore, it is respectfully proposed that the rejection of claim 91 for anticipation by the Archer et al., reference is overcome.

Likewise, claim 96 recites several elements not present or suggested in any of the teachings of Archer et al., including:

a) performing a biopsy or other cell selection technique to obtain cells to establish a second non-human differentiated somatic cell or cell-line from said first transgenic animal;

b) characterizing said second non-human differentiated somatic cell or cell-line using known molecular biology methods to ensure that the selected said second non-human differentiated somatic cell or cell-line is at least heterozygous for said first DNA sequence; and

and

c) performing a second nuclear transfer procedure with at least one of said second non-human differentiated somatic cells to produce at least a second transgenic animal at least heterozygous for said first DNA sequence.

None of the elements a-c above are disclosed in the Archer et al., reference. Therefore, it is respectfully proposed that the rejection of claim 96 for anticipation by the Archer et al., reference is overcome.

Claims 31, 34, 48-55, 60, 61, 65-73, 86-90 and 94-95 are canceled herein. Dependent claims 35-43, 56-58 and 92-93 being dependent upon and further limiting independent claim 96, should also be allowable for that reason, as well as for the additional recitations they contain. Reconsideration of the rejection of amended claims 35-43, 56-58 and 91-93 under 35 U.S.C. § 102(b), is respectfully requested.

New claims 96 - 119 are dependent upon independent amended claims 96 or 91 as the case may be. As they retain all the elements of the amended base claims from which they

depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 96 - 119 under 35 U.S.C. § 102(b), in view of the above amendments and remarks.

Strelchenko et al.,

Claims 31, 34-44, 47-58, 60, 61, 65-73, 86-88 and 90-95 are rejected under 35 U.S.C. §102(e) as being anticipated by Strelchenko et al. (U.S. Patent No. 6,011,197, hereinafter referred to as the '197 patent). This rejection of the claims, as amended, is respectfully traversed.

As stated above with regard to Strelchenko et al., to avoid rejection for anticipation, it is only necessary to show that a claim contains at least one element not disclosed in a single prior art reference. Therefore, in order to avoid rejection for anticipation, it is only necessary to show that independent base claims 91 and 96 each contain at least one element not disclosed in Strelchenko et al. In reviewing the claims of the Strelchenko et al., reference, as guided by the prior legal precedent cited above, it is clear that the claims not only fail to recite the same elements, the actual function or "process" of utilizing the elements differs considerably. Rather, Strelchenko recites a "immortalized, totipotent cells," a single round of nuclear transfer and focus on the cloning requirements of bovines alone. These elements represent the prior art that relied on the generation of a transgenic fetus to provide a single clone that was then fully developed through natural gestation to provide a cloned adult. The current invention improves upon this technology by accelerating and making more efficient the cloning of a series of transgenic animals each of which was created by utilizing differentiated somatic cells and at least one round of nuclear transfer, preferably at least two rounds of nuclear transfer. Moreover, claim 91 recites at least two elements not present or suggested in any of the claims 1-29 of Strelchenko et al., including:

a) performing a nuclear transfer procedure with said non-human differentiated somatic cells to produce at least one transgenic mammal at least heterozygous for said first DNA sequence;

and

b) wherein said first DNA sequence encoding a desired gene is actuated by a tissue specific promoter.

Neither of the elements a nor b above are disclosed in the Strelchenko et al., reference. Therefore, it is respectfully proposed that the rejection of claim 91 for anticipation by the Strelchenko et al., reference is overcome.

Likewise, claim 96 recites:

a) performing a biopsy or other cell selection technique to obtain cells to establish a second non-human differentiated somatic cell or cell-line from said first transgenic animal;

b) characterizing said second non-human differentiated somatic cell or cell-line using known molecular biology methods to ensure that the selected said second non-human differentiated somatic cell or cell-line is at least heterozygous for said first DNA sequence; and

and

c) performing a second nuclear transfer procedure with at least one of said second non-human differentiated somatic cells to produce at least a second transgenic animal at least heterozygous for said first DNA sequence.

None of the elements a-c are disclosed in the Strelchenko et al., reference. Therefore, it is respectfully proposed that the rejection of claim 96 for anticipation by the Strelchenko et al., reference is overcome.

Claims 31, 34, 48-55, 60, 61, 65-73, 86-90 and 94-95 are canceled herein. Dependent claims 35-43, 56-58 and 92-93 being dependent upon and further limiting independent claim 96, should also be allowable for that reason, as well as for the additional recitations they contain. Reconsideration of the rejection of amended claims 35-43, 56-58 and 91-93 under 35 U.S.C. § 102(e), is respectfully requested.

New claims 96 - 119 are dependent upon independent amended claims 96 or 91 as the case may be. As they retain all the elements of the amended base claims from which they

depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 96 - 119 under 35 U.S.C. § 102(e), in view of the above amendments and remarks.

The Rejection Under 35 U.S.C. §103(a)

Archer et al., Amoah et al., and Strelchenko et al.

Claims 31, 34, 35, 37, 42-44, 47, 49, 54-58, 61, 65, 67, 72, 73, 86-88 and 90-95 are rejected under 35 U.S.C §103(a) as being unpatentable over Archer et al., and Amoah et al., in view of Strelchenko et al.. Claims 31, 34, 48-55, 60, 61, 65-73, 86-90 and 94-95 are canceled herein. Reconsideration of the rejection of amended claims 35-43, 56-58 and 91-93 under 35 U.S.C. § 103(a), is respectfully requested. Moreover, in light of the Examiner's very thorough comments it should be noted at the outset that all of the pre-existing claims have been amended herein to address a variety of the Examiner's concerns as well as to ameliorate some structural and grammatical problems with the claims and more fully present the invention. Therefore Applicant requests reconsideration of the claims in light of these extensive amendments and claim additions. Given the analysis below, the Examiner's remaining objections to the claims as amended are respectfully traversed.

At the outset it should be stated that Applicants purposefully employed a secretion system of incredible power and complexity (mammary epithelial cell lactation) that provides for the production and secretion of specific hormonally induced proteins (e.g., milk and milk proteins) in incredibly high concentration and pushes them out of the system of a whole animal in a regular reliable amount, in this way transgenic animals are quite unlike any other tool in the molecular biologists proverbial "tool kit." Not only did the Applicants use this system they increased its power and complexity by making an accelerated scale-up of the process possible.

As presented above neither Archer et al., nor Strelchenko provide any guidance along this line, and are in fact, completely silent with regard to any methods of enhancing the speed of cloning or nuclear transfer techniques.

Prior to the improvements provided by the Applicants the common practice of those skilled in the art was to attempt production of transgenic animals from transgenic animals

through natural gestation or use imprecise viral vectors to make a transgenic animal (Strelchenko et al., and Archer et al., respectively). These techniques are both time consuming and very different from the current teachings as recited in the claims. Any analysis that bases its rejection on the use of Strelchenko et al., on the premise that one transgenic expression protocol and all of the interplay in the various tools used to achieve expansion of a given transgenic 'herd' are alike is inappropriate.

Establishment of a *prima facie* case of obviousness is a procedural tool for allocating the burden of proof as between an Applicant and the Examiner. The initial burden is upon the Examiner to present this *prima facie* case of obviousness to negative patentability. Respectfully, in the current case and with the amended claims the Examiner has not had the opportunity to establish the needed case of obviousness, thus without more the Applicant is entitled to a grant of the patent. In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir.1992). For expediency, and to potentially preserve patent term Applicant however wants to provide the framework through which a review of the prior art must be approached.

A *prima facie* case of obviousness is established when the teachings from the prior art itself suggest the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d. 781, 26 U.S.P.Q. 1529 (Fed. Cir. 1993); In re Rijckaert, 28 U.S.P.Q.2d 1955 (Fed. Cir. 1993). The basic considerations which apply to obviousness rejections under MPEP § 2141 are as follows:

(1) the claimed invention must be considered as a whole;
(2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
(3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
(4) reasonable expectation of success is the standard by which obviousness is determined.

When the prior art itself fails to meet even one of the above criteria the cited art does not satisfy 35 U.S.C. § 103(a) and prevents the establishment of the required *prima facie* case of obviousness by the Examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444

(Fed. Cir. 1992); In re Rijckaert, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). As pointed out above, the Archer et al., and Strelchenko et al., references not only fail to anticipate the current claims they also fail to render them obvious when taken alone or provide any incentive to combine with one another to build a case of *prima facie* obviousness.

Moreover, virtually all inventions are combinations of old elements. Respectfully therefore, even though an examiner or accused infringer may often find every element of a claimed invention in the prior art this does not in itself prevent patentability. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner or accused infringer to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc. 231 F.3d 1339; 56 U.S.P.Q.2D 1641 (Fed. Cir. 2000).

Additional Citation

Amoah *et al.* does not provide what Archer et al., and Stelchenko et al. lack. That is, Amoah *et al.,* must present the protocols and methods to accelerate the production of transgenic animals or explain the use of multiple rounds of nuclear transfer to bypass the regular gestation times required for the production of additional animals, this is does not do. Instead Amoah et al., provides a primer on artificial insemination in goats.

As with the other citations provided by the Examiner, respectfully, Amoah et al., cannot negative the instant claims when taken alone or when provided in the combination assembled by the Examiner. In addition it must be respectfully reiterated that each of the citations provided above fail to recognize, expressly or implicitly, any need, possibility or benefit of combining their disparate teachings in such a way that they might then read on the instant claims. Absent some teaching, suggestion, or incentive supporting this combination, a teaching that is simply not present in any of the citations provided by the Examiner, the references are incapable of supporting a obviousness rejection under § 103(a). Carella v. Starlight Archery, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

Respectfully, it is thus the objective measure of obviousness that the prior art cited of record is incapable of supporting, thus preventing the maintenance of a 35 U.S.C. §103(a) rejection. Applicants therefore respectfully request the withdrawal of the Rejection of amended claims 35-43, 56-58 and 91-93 under 35 U.S.C. § 103(a), as being unpatentable over Archer et al., Strelchenko et al., in view of Amoah et al., and under 35 U.S.C. §103(a).

New claims 96 - 119 are dependent upon independent amended claims 91 and 96 as the case may be. As they retain all the elements of the amended base claims from which they depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 96 - 119 under 35 U.S.C. § 103(a), in view of the above amendments and remarks.

Other than a fee for the extension of time, and a fee for additional claims no fee is deemed necessary in connection with the filing of this Amendment. However, the Commissioner is authorized to charge any fee which may now or hereafter be due for this application to GTC Biotherapeutics' Deposit Account No. 502092.

Applicants respectfully submit that the pending claims of this application are in condition for allowance, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, the Examiner is invited to telephone the undersigned at the number given below.

Early and favorable action is earnestly solicited.

Respectfully Submitted,

Date: 2/27/03

By: _____

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Claim Appendix

35. (Amended herein) The method of claim 96, wherein said transgene construct comprises a nucleic acid sequence encoding a human polypeptide.

36. (Amended herein) The method of claim 96, wherein said transgene construct is capable of knocking out the expression of a gene endogenous to said first transgenic animal.

37. (Amended herein) The method of claim 35, wherein said transgene construct further comprises a promoter wherein the nucleic acid is under the control of said promoter.

38. (Amended herein) The method of claim 37, wherein said promoter is a tissue specific promoter.

39. (Amended herein) The method of claim 38, wherein said tissue-specific promoter is a promoter preferentially expressed in mammary gland epithelial cells.

40. (Twice Amended) The method of claim 39, wherein said promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

41. (Amended herein) The method of claim 37, wherein said promoter is a caprine promoter.

42. (Amended herein) The method of claim 35, wherein said nucleic acid encodes a polypeptide selected from the group consisting of a hormone, an immunoglobin, a plasma protein, and an enzyme.

43. (Amended herein) The method of claim 35, wherein said nucleic acid encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate decarboxylase, a human serum albumin, a myelin basis protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a

lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α-1-antitrypsin.

56. (Twice Amended) The method of claim 96, wherein said second non-human differentiated somatic cell or cell-lines are fibroblasts.

57. (Twice Amended) The method of claim 56, wherein said fibroblasts are primary fibroblasts.

58. (Twice Amended) The method of claim 56, wherein said fibroblasts are primary derived fibroblasts.

91. (Twice Amended) A method of preparing a genetically engineered transgenic mammal, comprising:

(a) inseminating a first female non-human mammal recipient with semen from a transgenic non-human animal of the same species known to have a transgene present and expressed;

(b) obtaining a transgenic non-human embryo from said first female recipient;

(c) obtaining a somatic cell from said embryo;

(d) culturing said differentiated somatic cell in a suitable medium, such that a differentiated somatic cell line is obtained and,

(e) performing a nuclear transfer procedure with said non-human differentiated somatic cells to produce at least one transgenic mammal at least heterozygous for said first DNA sequence;

wherein said first DNA sequence encoding a desired gene is actuated by a tissue specific promoter.

92. (Amended herein) The method of claim 96, wherein said second non-human differentiated somatic cell or cell-line cells are obtained from an embryonic goat on or after day 10 of embryogenesis.

93. (Amended herein) The method of claim 96, wherein said second non-human differentiated somatic cell or cell line preparation is kept in an airtight container.

96. (New) A method for the accelerated production of transgenic animals comprising:

a) transfecting a first non-human differentiated somatic cell or cell-line with a transgene construct containing a first DNA sequence;

b) selecting a transfected cell or cell-line into which said first DNA sequence has been inserted into the genome of said first non-human differentiated somatic cell or cell-line;

c) performing a first nuclear transfer procedure to generate a first transgenic animal at least heterozygous for said first DNA sequence;

d) performing a biopsy or other cell selection technique to obtain cells to establish a second non-human differentiated somatic cell or cell-line from said first transgenic animal;

e) characterizing said second non-human differentiated somatic cell or cell-line using known molecular biology methods to ensure that the selected said second non-human differentiated somatic cell or cell-line is at least heterozygous for said first DNA sequence; and

f) performing a second nuclear transfer procedure with at least one of said second non-human differentiated somatic cells to produce at least a second transgenic animal at least heterozygous for said first DNA sequence.

97. (New) The method of claim 96, wherein said first transgenic animal is at an embryonic stage of development.

98. (New) The method of claim 96, wherein said first transgenic animal is at a fetal stage of development.

99. (New) The method of claim 96, further comprising developing said first transgenic animal into an adult non-human animal.

100. (New) The method of claim 96, wherein said first transgenic animal is a mammal.

101. (New) The method of claim 96, wherein said first DNA sequence encodes a desired protein;

102. (New) The method of claim 96, wherein the genetic composition of said first transgenic animal is characterized to confirm the presence and expression of the transgene.

103. (New) The method of claim 96, wherein said first nuclear transfer procedure further comprises transferring the nucleus of said transfected cell into a suitable enucleated recipient cell of the same species, thereby obtaining a reconstituted cell.

104. (New) The method of claim 96, wherein said first transgenic animal is biopsied so as to characterize the genome of said first transgenic animal.

105. (New) The method of claim 96, wherein at least one of the cells from said second non-human differentiated somatic cell or cell-line is expanded through cell culture techniques

for use in said second round of nuclear transfer so as to produce a multiplicity of animals transgenic for said DNA of interest.

106. (New) The method of claim 100, wherein the source of said differentiated somatic cell or cell-line is an ungulate.

107. (New) The method of either claims 106, wherein said differentiated somatic cell or cell-line is from an ungulate selected from the group consisting of bovine, ovine, porcine, equine, caprine and buffalo.

108. (New) The resultant offspring of the methods of claim 107.

109. (New) The method of claim 96 wherein said first DNA sequence codes for a biopharmaceutical protein product.

110. (New) The method of claim 109 wherein said first DNA sequence encoding a desired gene is actuated by at least one beta casein promoter.

111. (New) The resultant milk derived from the offspring of the methods of claim 108.

112. (New) The method of claim 96, wherein said second non-human differentiated somatic cell or cell-line is obtained from said first transgenic animal by known tissue dissociation means including enzymatic means and/or mechanical means.

113. (New) The method of claim 96, wherein said second non-human differentiated somatic cell or cell-line is selected from a group of cell types present in said first transgenic animal including:

a) fibroblasts

b) cumulus cells

c) neural cells

d) mammary cells; and

e) myocytes.

114. (New) The resultant offspring of the methods of claim 91.

115. (New) The method of claim 91 wherein said transgene codes for a biopharmaceutical protein product.

116. (New) The method of claim 115 wherein said tissue specific promoter is a beta casein promoter.

117. (New) The resultant milk derived from the offspring of the methods of claim 114.

118. (New) The method of claim 91, wherein said second non-human differentiated somatic cell or cell-line is obtained from said first transgenic animal by known tissue dissociation means including enzymatic means and/or mechanical means.

119. (New) The method of claim 91, wherein said second non-human differentiated somatic cell or cell-line is selected from a group of cell types present in said first transgenic animal including:

a) fibroblasts

b) cumulus cells

c) neural cells

d) mammary cells; and

e) myocytes.